REMARKS

1. Discussion of Claims

Claim 1 has been amended. The term "acute" has been added to the claim in view of the Examiner's rejection of the claim as failing to comply with the enablement requirement. The basis for the amendment is found on page 12, lines 29-30.

Claim 5 has been amended. The sentence "in a plurality of separate dosings" has been deleted based on the Examiner's rejection of the claim regarding new matter. The phrase "as a single dosage, regular or continued administration, or as a sequential administration" has been added. The amended claim corresponds to the claim 5 as originally filed. Basis in the description is found on page 14, lines 16-18.

Claim 30 has been amended. In accordance with the Examiner's opinion on enablement for alpha-MSH equivalents of the invention comprising the sequence His-Phe-Arg-Trp, the terms "-Trp" and "(amino acids 6-9 of SEQ ID NO:1)" have been added, so the alpha-MSH equivalent of the invention is a peptide comprising the sequence His-Phe-Arg-Trp. The basis for this amendment is found in previous claim 33. Strictly speaking, the application only requires His-Phe-Arg (on page 16, lines 31-34). Nevertheless, as all analogues of interest also comprise Trp, the inventors are prepared to accept the limitation proposed, without prejudice or disclaimer to seek broader claims in a continuation application similar amendments have been made to claim 42.

Claim 35 has been amended to be dependent on new claim 44.

Claim 37 has been amended to be dependent on claim 28. The terms "further comprising administration of an anti-inflammatory amount of an alpha-MSH equivalent which is a peptide comprising the sequence Lys-Pro-Val, which peptide binds to an alpha-MSH receptor and/or a melanocortin receptor, and thereby exercises anti-inflammatory activity, which is a" and "consisting of" have

been deleted. The terms " wherein the" and "further comprising" has been added. Thus, the term "further comprising" has been used instead of "consisting of".

Claim 38 has been amended to be dependent on claim 28. The terms "further comprising administration of an anti-inflammatory amount of an alpha-MSH equivalent which is a peptide comprising the sequence Lys-Pro-Val, which peptide binds to an alpha-MSH receptor and/or a melanocortin receptor, and thereby exercises anti-inflammatory activity, which is a" and "consisting of" have been deleted. The terms " wherein the" and "further comprising" has been added. Thus, the term "further comprising" has been used instead of "consisting of".

Claim 41 has been amended. The term "equivalent" has been added. Basis is found on page 16, lines 32-34 in the specification.

Claim 30 also now contains limitation (b) of claim 31, for consistency with new claims 44 and 45. Similar amendments were made to claims 28 and 36.

Claims 44 and 47 recite the presence of homo Phe or halogenated Phe. This is based on pp. 16-17 of the specification, amended on September 20, 2004 to explicitly recite disclosure previously incorporated by reference to WO96/41815 and USP 5,830,994.

Claims 45 and 49 recite the presence of one or more D-amino acids, and have the same basis as claim 44.

Claim 46 recites the presence of the sequence Lys-Pro-Val; there is basis at page 17, line 2. Claim 50 identifies the peptide as a fragment of α-MSH. It is therefore helpful to recite the sequence of α-MSH, which is:

Ser-Tyr-Ser-Met-Glu-**His-Phe-Arg-Trp**-Gly-**Lys-Pro-Val**.

Claims 31-34 and 43 have been cancelled.

2. Enablement Rejections

2.1. Claims 1 and 20 have been rejected under what appears to be utility/enablement grounds, properly presented as a dual rejection under 35 USC §101 and §112, para. 1. The rejection is respectfully traversed. The Examiner's reasoning is inapplicable because claim 1, as amended, refers to treatment of acute inflammation, and our animal model is proper for this indication.

We fully agree with the Examiner's point of view that the experimental model of acute lung inflammation induced by LPS inhalation is not a model for a chronic condition such as chronic obstructive pulmonary disease (COPD). But the model of acute lung inflammation induced by LPS inhalation is a proper model for exacerbations in COPD. An exacerbation is defined as an acute worsening of a condition. Thus, it must be emphasized that the model of acute lung inflammation induced by LPS inhalation is a model for an acute temporary condition in COPD.[1]

Exacerbations in COPD can clinically be defined as a complex of respiratory symptoms (i.e. new onset or worsening of more that one symptom such as cough, sputum, dyspnea or wheeze) lasting for at least 3 days. During exacerbations in COPD an acute inflammatory response with eosinophil and neutrophil infiltrations are observed in the lungs (Am. J. Respir. Crit. Care Med. 150:1646-1652, 1994). The experimental model used by the inventors mimics this inflammatory response in the lungs.

Thus, in accordance with the outlined argumentation, what is now claimed is: "1. A method for the treatment or prophylaxis of a non-ischemic condition characterized by acute inflammation of the lung and airway, the method comprising administering a therapeutically or prophylactically effective amount of an erythropoietin EPO to the individual in need thereof." In claim 20, it is specified that the condition characterized by acute

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[1] In the September 20, 2004 amendment, p. 14, we should have identified the LPS inhalation model as one for exacerbations in COPD.

inflammation of the lung and airway is exacerbations in COPD. It is respectfully submitted that the model of acute lung inflammation is a widely used model for studying exacerbations in COPD evidenced by the high number of publications describing the model.

To further substantiate our argumentation outlined above, we submit a declaration by an expert in the field of anaesthesiology, critical care- and pulmonary medicine stating that the experimental model of acute lung inflammation induced by LPS inhalation is in fact a widely used model for exacerbations in COPD.

2.2. To meet the Examiner's objections regarding scope of enablement for the a-MSH equivalents according to the invention, the a-MSH equivalents have been restricted to equivalents comprising (a) the sequences His-Phe-Arg-Trp and/or Lys-Pro-Val or (b) D-amino acid mutants thereof.[2]

It is respectfully submitted that by this amendment the a-MSH equivalents of the invention have a common structural feature with a relation to function which is well known to a person of ordinary skill in the art and that the person of ordinary skill in the art on the basis of publicly available literature and the disclosure in the patent application will be able to perform the invention over the whole area claimed without undue experimentation and without needing inventive skill.

3. Written Description Issues

Claims 1 and 5 have been rejected for failing to comply with the written description. However, no specific criticism of claim 1 is offered. With regard to claim 5, the examiner questions "is administered in a plurality of separate dosings". Claim 5 has been amended to revert to the wording of original claim 5, which

[2] We also allow for certain Phe modifications.

necessarily is part of the original description.

4. Definiteness Issues

Claims 37-43 have been amended to recite that the peptide further comprises A1-B2-C3-D4 (37) or R1-W-X-Y-Z-R2 (38), which does not conflict with them comprising Lys-Pro-Val as required by base claim 28.

5. Prior Art Issues

5.1. Claims 1, 2, 23, and 29 stand rejected as anticipated by Akamatsu. We traverse.

The Examiner states that Akamatsu *et al.* describes the administration of human EPO for treatment of the anemia of malignant tumors.

The Examiner argues that the mouse model used in Akamatsu *et al.* (Lewis lung carcinoma mouse model) would exhibit inflammation of the lung or airways, and thus that the condition to be treated is a non-ischemic condition characterized by inflammation. However, the condition to be treated in Akamatsu is anemia and NOT the malignant tumors. Akamatsu *et al.* states: "The present invention relates to a pharmaceutical composition for the treatment of the anemia of malignant tumors that comprises a therapeutically effective amount of human erythropoietin..." column 1, lines 6-9.

The anemia is a symptom of the malignant tumor. However, you do not treat the underlying disease by treating the symptoms of the disease. For example, you could have a headache due to a brain tumor and receive pain relievers for the headache. However, you do not treat the patient for the brain tumor by administering pain relievers.

At the time of Akamatsu's filing, there was doubt whether this malignancy-induced anemia would be responsive to EPO, as it was uncertain whether it was due to impaired EPO production (as

opposed to hyperresponsiveness to EPO). Col. 1, lines 58-67. Nonetheless, Akamatsu persisted with the attempt to treat malignancy-associated anemia with EPO. Akamatsu *et al.* states, column 2, lines 10-12, "EPO turned [sic] very effective against the anemia, and therefore, the inventors concluded that they are useful as therapeutic agents for the treatment of anemia in malignancy. The present invention has been accomplished on the basis of this finding." column 2, lines 16-21.

Thus, the objective for the EPO treatment in Akamatsu *et al.* is alleviation of anemia. Anemia cannot be viewed as a condition characterized by acute inflammation of the lung and airways. Consistently, Akamatsu et al. does not demonstrate any anti-inflammatory effects of EPO. Hence, Akamatsu *et al.* do not anticipate the present invention

Furthermore, Akamatsu et al. gives no hints or indication that the administration of EPO should have other effects than treating the anemia, such as being effective against the malignant tumor.

5.2. Claims 1, 26-31, 36, 40 and 43 stand rejected as obvious over Akamatsu et al. in view of Hernandez et at.
The Examiner argues that Akamatsu *et al.* describes the use of EPO and Hernandez *et al.* the use of a-MSH for the same purpose and thus that it is prima facie obvious to combine the two compositions in a third composition.

According to the Examiner, the references demonstrate the use of EPO and a-MSH, respectively, for the treatment of a non-ischemic condition characterized by inflammation of the lung or airways. Thus, the Examiner argues that it would be obvious to one skilled in the art to combine the two compounds.

We do not agree that the two references describe the use of EPO and a-MSH, respectively, for the same purpose. As outlined above, Akamatsu *et al.* describes the treatment of anemia, which cannot be considered as a condition characterized by acute

inflammation of the lung and airways.

We find Akamatsu *et al.* to be without relevance for the present invention as the aim of the reference belongs to another field, i.e. treatment of anemia.

Hernandez Delgado et al. shows that alpha-MSH may have an effect on myeloperoxidase in LPS-induced lung inflammation, which suggests that alpha-MSH treatment may have an effect that could be associated with inhibition of neutrophils. However, the paper provides no data supporting that EPO could have anti-inflammatory effects in inflammatory lung disease.

Obviously, none of the prior art documents disclose or suggest that EPO in combination with alpha-MSH treats or prevents an inflammatory condition under non-ischemic conditions in lung and airways. Therefore, there is no incentive for the person skilled in the art to combine Akamatsu *el al.* with Hernandez *et al.* The person skilled in the art finds no hints or suggestions in either of the references to each other.

Thus, in light of the prior art documents, a person skilled in the art would not have been encouraged to use EPO in combination with alpha-MSH for the treatment of an acute inflammatory condition under non-ischemic conditions in the lung and airways. Claim 1 and the claims dependent thereon thus are both novel and involve an inventive step.

6. Compliance with Sequence Rules

Claims 32, 33 and 38 were questioned (p. 13) as allegedly failing to comply with the sequence rules. Claims 32 and 33 have been cancelled.

With regard to claim 38, the sequence rules apply only if there are at least four "specifically identified" amino acids. In the claim 38 sequence, R1 and R2 have a variable number of AAs, and W, X, Y and Z denote non-specifically identified amino acid positions. In particular, "W" can be L-His or D-His, "X"

has five possibilities, "Y" can be L-Arg or D-Arg, and "Z" can be L-Trp or D-Trp. In R1, the amino acid proximal to "W" can be Gly or Glu, so R1 does not present any specifically identified AAs. R2 presents at most two specifically identified AAs (Gly-Lys). A specifically identified position is one at which only one amino acid is permitted (exceptions made for Asx and Glx), see MPEP 2422.02 at page 2400-33. Xaa can be used to represent D-amino acids, but the Xaa denotes a choice between an L- and a D-amino acid, when the position is not "specifically identified".

Respectfully submitted,

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-Declaration

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